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Original article

Efficacy of tobramycin aerosol in nasal polyposis

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ABSTRACT

Context: Treatment of infected nasal polyposis.
Material and methods: Multicenter interventional prospective double-blind randomized study with matched groups: treatment with tobramycin aerosol versus isotonic saline aerosol. The study population included 55 patients: 23 receiving isotonic saline aerosol and 32 receiving tobramycin. A novel device (Easynose®) was used with an original principle limiting pulmonary deposition and ensuring homogeneous peripheral deposition in the nasal cavities.
Objectives: The principal objective was to compare bacteriological eradication between tobramycin 150 mg/3 ml versus isotonic saline, both administered by nebulization via the Easynose® device.
Results and conclusion: Tobramycin aerosol administered via the Easynose® device showed significantly better bacteriological eradication than isotonic saline.

1. Introduction

Nasal polyposis (NP) is a chronic inflammatory disease of the sinonasal mucosa, with prevalence of about 4% [1]. It is characterized by essentially bilateral ethmoid and nasal cavity polyps [2].

The few bacteriological studies of NP are concordant, showing 70–80% of cultures pathogen-positive [3–5]. Isolates mainly comprise *Staphylococcus aureus* (40–60% of samples), *Pseudomonas aeruginosa* (approx. 5%), *Haemophilus* spp. (approx. 5%), and *Streptococcus pneumoniae* (approx. 5%) [4,5]. These rates are the same in operated and non-operated patients. The isolates are susceptible to tobramycin [3–5]. However, NP course features infectious episodes associating heightened sinus secretion and abundant purulent secretion in the nasal cavity [2,3]. These episodes are presently treated by wide-spectrum systemic antibiotics, sometimes associated to oral corticosteroids. No published studies have demonstrated the efficacy of such treatment, and there are no published guidelines.

Notably, there are no published data regarding the efficacy of any kind of nebulization aerosol therapy in rhinosinus pathologies, whether acute or chronic, despite the fact that this mode of administration seems especially well suited by virtue of the easy access to the nasal and sinus cavities [6]. It seems particularly suited to patients undergoing bilateral ethmoidectomy for NP, in view of the wide opening of the sinuses. A new device was recently developed by the Diffusion Technique Française company (Easynose®), based on an original principle (patent No. FR2938770) that reduces pulmonary deposition and ensures homogeneous peripheral deposition in the nasal cavities [7].

In the light of these data and this recent innovation, we performed a prospective multicenter study in France to assess the contribution and limitations of nebulization of tobramycin solution in infection following surgery for NP.

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2. Material and methods

2.1. Methods

2.1.1. Study design

A prospective interventional study randomized patients into two matched groups (tobramycin versus isotonic saline nebulization) in a double-blind comparative multicenter design. Randomization was balanced (ratio 1:1), based on a list comprising size-4 blocks. Patients randomly received either tobramycin (group B) or isotonic saline (group A). The local review board (*Comité de Protection des Personnes* [CPP] Île-de-France VIII) approved the research protocol on October 8, 2010.

2.1.2. Treatment

The active treatment was a solution of 150 mg tobramycin for inhalation by nebulization in a single dose of 3 ml medium (150 mg/3 ml), administered by the Easynose® mesh nebulizer. The solution was composed of tobramycin 150 mg, water for injection qs 3 ml, and NaCl. The isotonic saline solution comprised the excipient of the active treatment. Active treatment or saline was administered twice daily for 7 days. Long-course corticosteroid therapy was allowed on condition that there had been no change in dosage for at least 1 month before inclusion. For the duration of the study, patients were not to have any nose-wash with physiological saline, antibiotherapy or systemic corticotherapy.

2.1.3. Study objectives

The principal study objective was to compare bacteriological eradication efficacy between tobramycin 150 mg/3 ml solution versus isotonic saline, both prepared for inhalation by aerosol nebulization using the Easynose® device.

Secondary objectives were:

- to compare efficacy between tobramycin 150 mg/3 ml solution versus isotonic saline, both prepared for inhalation by aerosol nebulization using the Easynose® device, in terms of clinical improvement, adverse effects and study withdrawal
- to analyze the acceptability of aerosol nebulization for the patient.

2.1.4. Study variables

To explore the principal objective, bacteriological analysis was performed on D0 and D10, following Day et al. [5], studying the presence of pathogenic strains in culture and their antibiotic susceptibility, with cytological analysis of the presence and concentration of leukocytes (D0 and D10).

Variables exploring the secondary objectives were:

- clinical: nasal congestion, anterior and posterior rhinorrhea, facial pain and heaviness, and olfactory impairment, assessed at D0, D10 and D30 on visual analog scales (VAS);
- acceptability: satisfaction in terms of ease of use of the device (preparation, inhalation) and duration of application.

Compliance was assessed in terms of failures to take treatment, reported on a self-assessment questionnaire filled out at the treatment sessions from D1 to D7, also reporting adverse effects. General clinical examination and fiberoptic endoscopy were performed at D0, D7 and D30.

2.1.5. Statistical analysis

Statistical analysis was blind, the two groups being labeled A and B (in fact, saline and tobramycin, respectively), identified only after the analysis results were in.

Table 1
Comparison of patient data per group. Differences were not significant.

	Group A Saline	Group B Tobramycin	*P*
n	23	32	
Mean age (range) in years	53 (29–70)	46 (22–70)	NS
Gender (% male)	43.48	53.13	NS
Time from NP diagnosis (years)	10	13	NS
Time from ethmoidectomy (years)	5	6	NS
% NP + asthma	17.39	28.13	
% Widal	39.13	37.50	NS

NS: non-significant.

Comparison used:

- Fisher exact test for qualitative data (gender, bacteriology);
- Student *t*-test or non-parametric Wilcoxon test for continuous quantitative data (age, time from NP diagnosis, time from last infection episode, time from ethmoidectomy, pre-treatment VAS);
- Wilcoxon test for ordinal qualitative data (bacteriological quantification of strains; cytological quantification of leukocytes).

2.2. Material

Inclusion criteria were patient:

- aged 20–70 years, with health insurance cover, consenting to the study;
- presenting with NP operated on for an episode of infection (aggravation of symptoms, with bilateral purulent secretion) within the previous 3 months;
- with fully healed total ethmoidectomy performed at least 2 months previously;
- without local or systemic antibiotherapy during the previous month;
- with NP not extending beyond the roof of the maxillary sinus.

Exclusion criteria were: pregnancy, breast-feeding, cystic fibrosis, proven ciliary dyskinesia or known immune deficiency, kidney failure and contraindications for aminoglycosides.

In all, 72 patients were randomized: 33 to group A (saline) and 39 to group B (tobramycin). Ten patients (6 in group A, 4 in group B) were excluded for negative D0 bacteriology, and 7 (4 in group A and 3 in group B) for major protocol deviation (age > 70 years, use of forbidden medication). Thus the final study population comprised 55 patients: 23 patients in group A, 32 in group B.

Table 1 presents patient data per group; characteristics were comparable ($P > 0.05$). Table 2 presents sinonasal status: symptoms, septum status, inferior turbinate status, polyposis volume, severity of purulence; characteristics were comparable.

Table 3 presents percentage positive culture per group; there was no significant difference. Table 4 presents cytologic results analyzing secretions; there was no significant difference. Table 5 presents the tobramycin susceptibility of isolates: 62 of the 70 strains were tobramycin-susceptible (88.57%), being mainly streptococci, which are naturally non-susceptible to aminoglycosides. Among the pathogenic strains, only one *S. aureus* strain had acquired tobramycin resistance.

3. Results

3.1. Compliance

Mean compliance was excellent in both groups: 98.9% in group A and 97% in group B. There were only 5 failures to take tobramycin.

Table 2
Comparison of pre-treatment (D0) clinical data per group. Differences were not significant.

D0	Group A Saline	Group B Tobramycin	*P*
n	23	32	
Nasal congestion[a]	45.22	41.72	NS
Anterior rhinorrhea[a]	37.17	33.50	NS
Posterior rhinorrhea[a]	62.87	50.69	NS
Sneezing[a]	21.78	19.69	NS
Facial pain[a]	28.39	25.00	NS
Olfactory impairment[a]	79.57	71.19	NS
% septal deviation	8.70	6.25	NS
% inferior turbinate hypertrophy	3.70	15.63	NS
% polypoid obstruction of the ethmoid[b]	32.65	33.72	NS
Quantification of purulent secretion[c]	49.26	53.19	NS

NS: non-significant.
[a] VAS: 0 (no discomfort) to 100 (intolerable discomfort).
[b] VAS: 0 (absent) to 100 (complete obstruction up to maxillary sinus roof).
[c] VAS: 0 (absent) to 100 (severe).

Table 3
Comparison of pre-treatment (D0) bacteriological data per group. Differences were not significant.

n (%) positive culture at D0	Group A Saline	Group B Tobramycin	*P*
n total	23	32	
Staphylococcus aureus	14 (60.87%)	19 (59.37%)	NS
Streptococcus pneumoniae	2 (8.70%)	5 (15.64%)	NS
Streptococcus group A	2 (8.70%)	2 (6.25%)	NS
Streptococcus group C	2 (8.70%)	0	NS
Branhamella catarrhalis	1 (4.35%)	1 (3.13%)	NS
Haemophilus influenzae	5 (21.74%)	6 (18.75%)	NS
Enterobacteria	4 (17.4%)	3 (9.37%)	NS
Pseudomonas aeruginosa	5 (21.74%)	1 (3.13%)	NS
Other strictly aerobic G-bacteria	0	4 (12.5%)	NS

NS: non-significant.

3.2. Bacteriological efficacy (D10)

Table 6 presents strain eradication. 46.88% of strains present at D0 had been eradicated by D10 in group B (tobramycin), versus 17.39% in group A (saline) ($P = 0.02$) (Fig. 1).

Table 4
Comparison of pre-treatment (D0) cytological data per group (% leukocyte presence in secretions). Differences were not significant.

% presence at D0	Group ASaline	Group BTobramycin	*P*
No leukocytes	23.81	36.67	
Few leukocytes	28.57	30.00	
Some leukocytes	23.81	6.67	
Many leukocytes	14.29	20.00	
Very many leukocytes	9.52	6.67	0.40

Table 5
Tobramycin susceptibility of D0 isolates.

% positive samples at D0	Resistant	Susceptible	Intermediate	Total
Staphylococcus aureus	1	32	0	33
Streptococcus pneumoniae	2	0	5	7
Streptococcus group A	0	0	4	4
Streptococcus group C	1	0	1	2
Haemophilus influenzae	0	11	0	11
Enterobacteria	0	7	0	7
Pseudomonas aeruginosa	0	6	0	6
Total	4	62	4	70

Table 6
Comparison of post-treatment (D10) bacteriological data per group (% positive culture). Differences were significant ($P = 0.02$).

% positive samples at D10	Saline	Tobramycin
Staphylococcus aureus	52.17	18.75
Streptococcus pneumoniae	13.04	7.81
Streptococcus group A	6.52	0
Streptococcus group C	4.35	0
Branhamella catarrhalis	4.35	0
Haemophilus influenzae	13.04	6.25
Enterobacteria	6.52	3.13
Pseudomonas aeruginosa	17.39	1.56

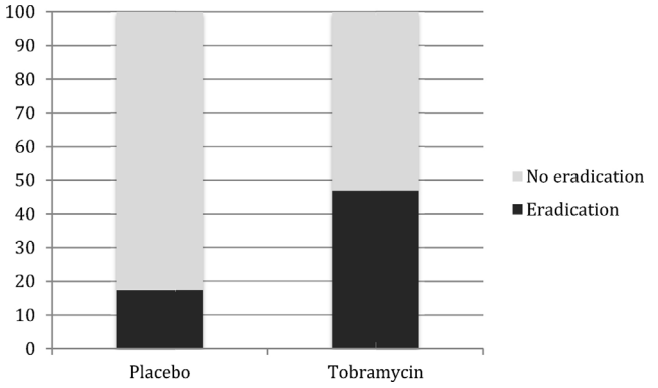

Fig. 1. Percentage bacterial eradication at D10; the difference between the two groups was significant ($P = 0.02$).

3.3. Clinical efficacy (D10 and D30)

There were no significant differences in symptoms between D0 versus D10 or D30: congestion, anterior or posterior rhinorrhea, sneezing, facial pain or olfactory impairment.

3.4. Early withdrawal

One patient in group A and 4 in group B withdrew from the study; this difference was not significant ($P = 0.38$). Reasons for withdrawal were: lack of clinical improvement ($n = 1$), loss to follow-up ($n = 1$), and need for forbidden treatment (notably for asthma) ($n = 3$).

3.5. Adverse events

There were in all 27 adverse events, none of which were serious. The rate of adverse events did not differ between groups ($P = 0.58$). Adverse events mainly comprised lower respiratory issues (asthma attack, cough, bronchitis), otologic issues (otalgia, otitis), gastrointestinal issues (diarrhea, nausea) and erythematous skin lesions.

3.6. Aerosol device use

Preparing the substance to be put in the aerosol device was found easy or very easy by 85.18% of patients in group A and 100% of patients in group B (non-significant). Using the device for inhalation was found easy or very easy by 100% of patients in both groups. Mean duration per application was 9 minutes 50 seconds in group A and 10 minutes in group B (non-significant).

4. Discussion

Inflammatory and infectious episodes associated with nasal polyposis are problematic due to their recurrence [2]. The

present attitude, in the absence of evidence, is based on oral antibiotherapy, or oral corticosteroids in severe cases impairing quality of life. There are no official guidelines.

The adverse side-effects of iterative oral corticosteroids have been assessed and notably include risk of osteoporosis and kidney failure [8]; prescription is limited to not more than 2 short courses in a given year. The adverse side-effects of iterative systemic antibiotics consist in increased bacterial resistance, which is becoming a major medical problem. In NP, prescription of these two classes of systemic medication should therefore be limited. In the early 2000s, corticosteroids prepared for nasal pulverization came onto the market, representing a significant advance as they show few systemic effects [9]. The problem of treating infection episodes, however, remained. The development of a novel device, Easynose®, with limited lung deposition and guaranteed homogeneous peripheral deposition in the nasal and sinus cavities [7], offers the possibility of aerosol therapy for drug-resistant ethmoid cavity infection following ethmoidectomy for NP. This was the focus of the present study.

Tobramycin was selected in the light of a previous study that highlighted the very particular bacteriology of the sinonasal cavities in patients operated on for NP [5]: 144 out of 120 samples (95%) were positive on culture. However, 12 of the 60 patients (20%) were colonized exclusively by non-pathogenic bacteria (coagulase-negative staphylococcus, *Corynebacterium* spp., etc.); thus only 102 samples (80% of patients) were colonized by pathogens. The present study found comparable positive culture rates and strain distributions (Table 3). The pathogens isolated were:

- Gram-positive bacteria: predominantly *S. aureus*, plus *S. pneumoniae* and group-G streptococci;
- Gram-negative bacteria: *B. catarrhalis*, *H. influenzae* and enterobacteria;
- strictly aerobic Gram-negative bacteria (e.g., *P. aeruginosa*), and other aerobic Gram-negative bacteria.

In the previous study, almost 94% of isolates were tobramycin-susceptible, and the present study found a very similar rate. Tobramycin delivered by aerosol has been fully studied in children with cystic fibrosis, showing good clinical and bacteriological results, leading to market authorization [10,11]. These findings led to administration of tobramycin by the Easynose® inhaler.

The study inclusion criteria (fully healed total ethmoidectomy at least 2 months previously) ruled out patients in the immediate postoperative period and those in whom NP volume could hinder ethmoid cavity deposition. Extension restriction to the roof of the maxillary sinus was logical, to ensure diffusion of the antibiotic and easy detection on fiberoptic nasal endoscopy in consultation. Excluding local and general antibiotherapy within 1 month of inclusion was intended to rule out any doubt as to the effect of the study aerosol therapy. To ensure a homogeneous population, patients with cystic fibrosis, proven ciliary dyskinesia or known immune deficiency were excluded. Finally, 10 patients were excluded secondarily (6 in group A and 4 in group B) for lack of D0 bacteriological findings (sterile culture), preventing assessment of the effect of the antibiotic; this was a low rate of sterile culture (13.8%) for a bacteriological study of rhinosinus pathology, where sterile culture rates are often close to 20%.

The principal study objective was to assess the efficacy of bacteriological eradication by tobramycin 150 mg/3 ml in nebulization aerosol therapy versus isotonic saline, both delivered by the Easynose® device. The principal result was that tobramycin was significantly more effective than saline ($P = 0.02$) (Fig. 1). This was probably due to the very high mucosal concentration achieved by a nebulizer adapted to the sinonasal region.

The secondary objectives were:

- to demonstrate the superiority of tobramycin 150 mg/3 ml solution versus isotonic saline, both prepared for inhalation by aerosol nebulization using the Easynose® device, in terms of clinical improvement, adverse effects and study withdrawal;
- to demonstrate the acceptability of aerosol nebulization for the patient.

The first of these could not be achieved: despite better eradication with tobramycin, clinical scores at D10 and D30 did not show improvement. This was probably due to short follow-up (30 days), as increased sinonasal inflammation following infection in NP is slow to resolve. The second sub-objective was achieved: patients rated acceptability as excellent. No adverse events were severe, and were basically due to the natural evolution of disease (NP and asthma), not implicating treatment. Mean application time per inhalation session was about 10 minutes.

This was thus the first study to demonstrate the efficacy of aerosol antibiotherapy compared to saline administered by the same device. It was also the first to demonstrate the efficacy of nebulization aerosol therapy as a means of drug delivery in a specific pathology (NP), with a specific drug (tobramycin), using a specific inhaler (Easynose®). The lack of clinical improvement may be explained by the short follow-up (30 days) in an inflammatory disease in which symptoms are slow to resolve, sometimes requiring associated general corticotherapy. Adverse events were not severe, were the same in both groups, and were basically due to the natural evolution of disease during infection. Administration by aerosol was well accepted, both as easy to use and short (sessions not exceeding 10 minutes).

5. Conclusion

This was the first randomized comparative study assessing bacterial eradication by nasal nebulization of tobramycin in patients operated on for nasal polyposis. Tobramycin delivered by the Easynose® device showed significant benefit compared to saline. Local antibiotherapy for infection in patients operated on for severe NP can reduce prescription of systemic antibiotics, contributing to the fight against emergent antibiotic resistance.

Disclosure of interest

The present phase III study received funding from the French pharmaceutical company Erempharma. Data monitoring and analysis were performed by the Clinact company.

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